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REMARKS

The Examiner indicates that claims 1-24 are pending in the instant application and has rejected claims 1-24. Applicants respectfully point out that claims 3 and 4 were canceled in a preliminary amendment and response to the Restriction Requirement filed on October 31, 2002. Accordingly, Applicants have responded to this action as if claims 1, 2 and 5-24 are pending and claims 1, 2 and 5-24 have been rejected. Claims 16 and 18-24 have been canceled. Claim 17 has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-24 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for antisense inhibition of tumor necrosis factor

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receptor 1 expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of expression of tumor necrosis factor receptor 1; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection of the claims.

At the outset, Applicants point out that the specification as filed contains data showing *in vivo* pharmacological and therapeutic activity in animals of the antisense compounds of the instant invention. In a well-accepted animal model of liver injury and hepatitis, antisense compounds of the instant invention were shown to be active *in vivo* to prevent death of animals that would normally die of liver disease in the model. In fact, survival of mice was increased from 10% to 100% in the mice. The response of the animals was shown to be associated with reduction in expression of tumor necrosis factor receptor 1 as levels of tumor necrosis factor receptor 1 mRNA were reduced in these animals by 86% in animals treated with the antisense compounds as compared to control animals. These data clearly show the successful use *in vivo* of antisense compounds of the instant invention targeted to tumor necrosis factor receptor 1. Accordingly, the data provided in the

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specification as filed provide enablement for the *in vivo* use of antisense compounds of the instant invention.

Additionally, Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells or in animals in the instant invention would also occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies or *in vivo* studies in animals would not be predictive of activity in humans.

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The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that are taught in the specification as filed. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies or *in vivo* studies in animals would not be predictive of activity in humans. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper again describes advances such as those taught in the instant specification. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies or *in vivo* studies in animals would not be predictive of activity in humans.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the

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paper state that extrapolation from *in vitro* data or *in vivo* animal data to *in vivo* effects in humans is unpredictable.

The papers by Gewirtz et al. (1996) and Agrawal (1996) are older papers not relevant to the state of the art of antisense compounds in 2000, the filing date of the instant application. Both papers discuss in general terms issues that were related to older antisense technology. However, nowhere do these papers state that extrapolation from *in vitro* data or *in vivo* animal data to effects in humans is unpredictable.

However, in an earnest effort to advance the prosecution and facilitate the allowance of this case, Applicants have amended claim 17 and canceled claims 16 and 18-24. Applicants reserve the right to file a continuing application directed to the canceled subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Ojwang et al. (1997), in view of Baracchini et al. (US Patent 5,801,154). Applicants have assumed that the

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rejection actually applies to claims 1, 2 and 5-15, the only pending claims of the group cited by the Examiner. The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to target the listed region of TNFR1 with antisense and then incorporate the claimed modifications as taught by Baracchini et al. since Baracchini et al. teach that the coding region, of which the claimed target region is part, is taught to be a desirable target. The Examiner suggests that one of skill would have motivated by to modify the oligonucleotides of Ojwang et al. because they teach the desirability of such modifications and that TNFR1 is a mediator of inflammation and an attractive target for intervention. The Examiner suggests that an expectation of success is provided by Baracchini et al. Applicants respectfully traverse this rejection.

Ojwang et al. (1997) disclose that antisense oligonucleotide inhibition of TNFR1 is a useful tool in understanding the role of this protein in cytokine induction and cell proliferation. The paper discloses partial phosphorothioate antisense deoxyoligonucleotides containing C-5 propynyl or hexynyl derivatives of 2'-deoxyuridine which caused attenuation of TNFR1 mRNA and protein and inhibited TNF-alpha-induced expression of IL-6

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in MRC-5 cells. The oligonucleotides were targeted to the poly (A) signal site of TNFR1 mRNA while a uniform phosphorothioate oligonucleotide targeted to the translation initiation codon of TNFR1 had no effect. The fact that the oligonucleotide targeted to the translation codon site had no effect is an important point since the coding region contains this site. Therefore, this paper teaches away from the antisense as claimed which are limited to a region within the coding region. Further, this paper fails to teach or suggest antisense compounds as claimed which are targeted to a very specific region of SEQ ID NO: 1. Therefore, this primary reference fails to teach the limitations of the claims.

The secondary reference cited fails to overcome the deficiencies in teaching of the primary reference, either alone or when combined with the primary reference.

Baracchini et al. (US Patent 5,801,154) teach methods of modifying antisense oligonucleotides to enhance activity. However, nowhere does this patent teach or suggest antisense oligonucleotides as claimed targeted to a specific region within the sequence of TNFR1 of SEQ ID NO: 1, or any region of such a nucleic acid molecule. The mere teaching of the coding region as being a general target for antisense does not provide one of skill

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with the knowledge to target successfully the specific region as claimed.

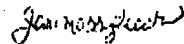
To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims, which claim antisense compounds targeted to a specific region of a specific SEQ ID NO., and thus cannot render the instant claimed invention obvious. Further, the reference of Ojwang et al. teaches that use of one oligonucleotide targeted to the beginning of the coding region is without activity, thus providing one of skill with doubt about success with other oligonucleotide targeted to the coding region. It is only with the specification in hand that one of skill would understand how to make and use the claimed antisense, in particular what region of the gene to target with antisense as now claimed. Withdrawal of this rejection is therefore respectfully requested.

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III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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